

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number
WO 2004/009145 A1

- (51) International Patent Classification⁷: **A61L 31/10**,
27/34, C08L 33/08, 33/10, 33/12, C08F 6/00, 6/08, 6/10
- (21) International Application Number:
PCT/US2003/021170
- (22) International Filing Date: 2 July 2003 (02.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
10/198,912 19 July 2002 (19.07.2002) US
- (71) Applicant: **ADVANCED CARDIOVASCULAR SYSTEMS, INC.** [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).
- (72) Inventors: **DING, Ni**; 4103 Cortona Court, San Jose, Ca 95135 (US). **ROORDA, Wouter, E.**; 36 Roosevelt Circle, Palo Alto, CA 94306 (US).
- (74) Agents: **KERRIGAN, Cameron et al.**; Squire, Sanders & Dempsey L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 2004/009145 A1

(54) Title: PURIFIED POLYMERS FOR COATINGS OF IMPLANTABLE MEDICAL DEVICES

(57) Abstract: A coating for a medical device, particularly for a drug eluting stent, is described. The coating includes a purified polymer such as a polyacrylate.

PURIFIED POLYMERS FOR COATINGS
OF IMPLANTABLE MEDICAL DEVICES

5 BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to coatings for implantable medical devices,
such as drug eluting vascular stents.

10

Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for
treating heart disease. A catheter assembly having a balloon portion is introduced
percutaneously into the cardiovascular system of a patient via the brachial or
15 femoral artery. The catheter assembly is advanced through the coronary
vasculature until the balloon portion is positioned across the occlusive lesion.
Once in position across the lesion, the balloon is inflated to a predetermined size
to radially compress against the atherosclerotic plaque of the lesion to remodel the
lumen wall. The balloon is then deflated to a smaller profile to allow the catheter
20 to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of
intimal flaps or torn arterial linings which can collapse and occlude the conduit
after the balloon is deflated. Moreover, thrombosis and restenosis of the artery
may develop over several months after the procedure, which may require another
25 angioplasty procedure or a surgical by-pass operation. To reduce the partial or

total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

A potential shortcoming of the foregoing method of medicating stents is that the polymers can contain impurities that trigger adverse biological responses

to the stent when implanted into a biological lumen. The polymers can contain impurities such as catalysts, initiators, processing aids, suspension aids, unreacted monomers and oligomers or other low molecular weight species, even though the polymer is sold as a "medical grade" polymer by the manufacturer. Thus, there is
5 a need for a stent coating with purified polymers. The present invention provides a coating to meet this need.

SUMMARY

In accordance with one aspect of the invention, a stent is disclosed that is
10 used for implantation in a vessel of a patient. The stent includes a coating which has a polymeric material which has been purified to be completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material. In one embodiment
15 of the invention, the polymeric material is a polyacrylate material. In another embodiment, the polymeric material is a blend of at least two polymers. In a further embodiment, the coating additionally has an active agent.

In accordance with a further aspect of the invention, a method of coating a stent is disclosed, including forming a coating having a polymeric material on the
20 stent, wherein the polymeric material has been purified to remove, or reduce the amount of, an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material. In one embodiment, the polymeric material is purified by a process including solvent

washing, centrifugal cleaning, soxhlet extraction, filtration, step precipitation, centrifugal filtration or a combination thereof.

In a further aspect, a method of coating a stent is disclosed including purifying a polymeric material to partially or completely remove an impurity or
5 impurities which can cause an adverse biological response, adding the purified polymeric material to a solvent to form a composition, applying the composition to the stent, and removing the solvent to form a coating including the purified polymeric material.

In yet another aspect of the present invention, a stent is disclosed with a
10 coating, the coating including a purified polymeric material that has generally the same degree of biological inertness as stainless steel when implanted in a blood vessel of a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Figures 1-4 are comparative spectrographs from a Fourier Transform Infrared Spectrophotometer as referred to in Example 2;

Figure 5 is a graph of percent stenosis from a 28 day animal study as referred to in Example 5; and

Figures 6 and 7 are histograms as referred to in Example 5.

20 DETAILED DESCRIPTION

For ease of discussion, the coatings and methods detailed herein will be described with reference to a coating for a stent. However, the implantable device coated in accordance with embodiments of the present invention may be any

suitable medical substrate that can be implanted in a human or veterinary patient. Examples of such implantable devices include self-expandable stents, balloon-expandable stents, stent-grafts, grafts (e.g., aortic grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g.,

5 FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," elastin (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold,

10 magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from

15 bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

Coating

In an embodiment of the present invention, a stent has a coating that includes a purified polymer. The polymer can be purified by methods detailed

20 herein. The stent can be used for implantation at a selected region of a vessel of a patient for inhibiting restenosis, and can include an active agent. After the polymer has been purified, the polymer is substantially biologically inert. "Purified" refers to a polymer that has had impurities removed or significantly reduced. "Impurities" refer to traces of catalysts, initiators, processing aids,

25 suspension aids, unreacted monomers and oligomers or other low molecular

weight species, or any other chemical remaining in the polymer, that can cause or effectuate an adverse biological response greater than which would occur if the impurity is removed or significantly reduced. For example, "medical grade" poly(*n*-butyl methacrylate) (PBMA) can contain impurities such as suspension
 5 aids (e.g., starch) and unreacted monomers. "Biologically inert" refers to a material that does not elicit a significantly greater adverse biological response than a biocompatible material, such as stainless steel, when implanted into a body vessel. Examples of biocompatible materials include metals such as stainless steel, titanium, and Nitinol, and organic materials such as collagen, fibronectin,
 10 polyethylene glycol, polysaccharides, TEFLON, silicone and polyurethane. As shown below in Example 5, it has been found that the polymeric coating of the present invention is essentially biologically inert.

The coating for a stent including the purified polymer can have a drug-polymer layer, an optional topcoat layer, and an optional primer layer. The drug-
 15 polymer layer can be applied directly onto the stent surface to serve as a reservoir for a therapeutically active agent or drug which is incorporated into the drug-polymer layer. The topcoat layer, which can be essentially free from any therapeutic substances or drugs, serves as a rate limiting membrane for controlling the rate of release of the drug. The optional primer layer can be applied between
 20 the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent.

According to one embodiment of the present invention, polymers of esters having the general formula (I):



25

(I)

or blends thereof, can be purified and then used for making the stent coatings.

In formula (I), X, X', and X'' are each, independently, a hydrogen atom (acrylates) or an alkyl group, such as a methyl group CH₃ (methacrylates); R, R' and R'' are each, independently, a C₁ to C₁₂ straight chained or branched aliphatic group, or a hydroxylated aliphatic group; "m" is an integer larger than 1, and "n" and "p" are each 0 or an integer. If both n = 0 and p = 0, the polymer of formula (I) is a homopolymer (i.e., PBMA). If n ≠ 0 and p = 0, or n = 0 and p ≠ 0, the polymer of formula (I) is a copolymer, and if n ≠ 0 and p ≠ 0, the polymer of formula (I) is a terpolymer.

After purification, polymers of formula (I) can be used for making either the drug-polymer layer, the topcoat membrane, the optional primer layer, or any combination thereof. For the purposes of the present invention, such polymers, or blends thereof, are defined as "polyacrylates" or as "polyacrylate materials."

One example of a polyacrylate suitable for fabricating either the drug-polymer layer or the topcoat membrane is PBMA, described by formula (I) where X = CH₃, n = 0, p = 0, and "R" is a *n*-butyl radical C₄H₉ (-CH₂-CH₂-CH₂-CH₃). PBMA has good biocompatibility, is soluble in many common solvents, has good mechanical and physical properties, and adheres well to the underlying stent surface or the primer layer. PBMA is available commercially from Aldrich Chemical Co. of Milwaukee, Wisconsin, and from Esschem, Inc. of Lynwood, Pennsylvania.

Some examples of polyacrylates that are suitable for purification and fabrication of the coating, e.g., the drug-polymer layer and/or the topcoat membrane, are summarized in Table 1.

Table 1

No.	Polyacrylate	Abbreviation	R	X	m	R'	X'	n/m	T _p °C
1	Poly(<i>n</i> -butyl methacrylate)	PBMA	<i>n</i> -C ₄ H ₉	CH ₃	>1	N/A	N/A	0	20
2	Poly(<i>iso</i> -butyl methacrylate)	P <i>i</i> -BMA	<i>i</i> -C ₄ H ₉	CH ₃	>1	N/A	N/A	0	66
3	Poly(<i>tert</i> -butyl methacrylate)	P <i>tert</i> -BMA	<i>tert</i> -C ₄ H ₉	CH ₃	>1	N/A	N/A	0	107
4	Poly(methyl methacrylate)	PMMA	CH ₃	CH ₃	>1	N/A	N/A	0	105
5	Poly(ethyl methacrylate)	PEMA	C ₂ H ₅	CH ₃	>1	N/A	N/A	0	63
6	Poly(<i>n</i> -propyl methacrylate)	PPMA	<i>n</i> -C ₃ H ₇	CH ₃	>1	N/A	N/A	0	35
7	Poly(methyl acrylate)	PMA	CH ₃	H	>1	N/A	N/A	0	9
8	Poly(<i>n</i> -hexyl methacrylate)	PHMA	<i>n</i> -C ₆ H ₁₃	CH ₃	>1	N/A	N/A	0	-5
9	Poly(methyl methacrylate-co- <i>n</i> -butyl methacrylate)	P(MMA-BMA)	CH ₃	CH ₃	>1	<i>n</i> -C ₄ H ₉	CH ₃	7/3	46
10	Poly(<i>n</i> -butyl methacrylate-co- <i>iso</i> -butyl methacrylate)	P(BMA- <i>i</i> -BMA)	<i>n</i> -C ₄ H ₉	CH ₃	>1	<i>i</i> -C ₄ H ₉	CH ₃	1/1	35
11	Poly(<i>n</i> -butyl methacrylate-co-2-hydroxyethyl methacrylate)	P(BMA-HEMA)	<i>n</i> -C ₄ H ₉	CH ₃	>1	CH ₂ CH ₂ OH	CH ₃	7/3	≥ 25
12	Poly(methyl methacrylate-co-2-hydroxyethyl methacrylate)	P(MMA-HEMA)	CH ₃	CH ₃	>1	CH ₂ CH ₂ OH	CH ₃	7/3	≥ 65
13	Poly(ethyl methacrylate-co-2-hydroxyethyl methacrylate)	P(EMA-HEMA)	C ₂ H ₅	CH ₃	>1	CH ₂ CH ₂ OH	CH ₃	7/3	>50

Only homo- and copolymers are listed in Table 1 (that is, the polymers of formula (I) where $p = 0$), but it should be understood that terpolymers corresponding to formula (I) (when $n \neq 0$ and $p \neq 0$) can be used as well. Also, it should be understood that the n/m ratios (from formula (I)) listed in Table 1 are provided by way of example, and other n/m ratios are contemplated to fall within the scope of this invention. For instance, the n/m ratio for P(BMA-HEMA) can also be 95/5.

Methods of Purification

Before the polymer is applied to the stent to form a coating, the polymer should be purified to remove impurities. By using the methods of the present invention, the polymer can be purified to remove a significant amount of residual catalysts, initiators, processing aids, suspension aids, unreacted monomers and oligomers or other low molecular weight species. For example, a polymer mass can be purified by washing the polymer mass with a solvent that dissolves the impurity, but not the polymer. Additionally, the polymer mass can be purified by dissolving the polymer mass in a solvent and subjecting the polymer mass to a centrifuge. According to other embodiments, the polymers can be purified by soxhlet extraction, filtration, step precipitation, and centrifugal filtration.

Solvent Washing

A solvent can be used to wash the impurities from the polymer. The impurities, such as low molecular species including unreacted monomers and oligomers, should be miscible in the solvent, while the polymer should be immiscible in the solvent. Representative examples of polymer-solvent pairs

include using methanol for PBMA, ethanol for PMMA, acetone or hexane for PEMA and methanol for P(BMA-HEMA).

The polymer should be mixed with the solvent and stirred. Sonication can also be used to mix the components. The polymer and solvent can be mixed for a few minutes to several hours, for example, from 1 to 16 hours. Usefully, the mixture is agitated for a relatively longer period to remove certain impurities. The mixed solvent can be replaced by fresh solvent so that the polymer can be washed multiple times. After the washing process is complete, the polymer is then dried (e.g., by vacuum drying) to remove the solvent from the polymer.

10

Centrifugal Cleaning

The polymer can also be purified by using a centrifuge if the impurity has a higher density than the polymer solution. The polymer is first substantially dissolved in a solvent. By way of example, PBMA can be dissolved in acetone.

Usefully, for many polymers, the solvent is a low density solvent (e.g., tetrahydrofuran (THF) or ethyl acetate). Many high density solvents such as chloroform, may not be useful for this particular process. Representative examples of polymer-solvent pairs include using ethyl acetate for PEMA, methyl ethyl ketone for PMMA and THF for P(BMA-HEMA).

After the polymer is dissolved in the solvent, the solution is centrifuged for about 10 minutes to 1 hour. The supernatant is carefully collected and the precipitate at the bottom of the centrifuge tubing, which contains impurities, is then removed from the solution. It is preferred that the solvent used for this process is the same solvent used for the stent coating process described in detail

below. Also, it is preferred to use this centrifugal cleaning process subsequent to the solvent washing process.

Filtration

5 Instead of using a centrifuge, impurities can be removed from the polymer by using filtration. The polymer should first be substantially dissolved in a solvent. The solvents useful for the centrifugal cleaning process are also useful for this process. The solution is then run through a filter connected to a vacuum pump to remove the impurities that do not dissolve with the polymer. The filter
10 used should have a pore size large enough to allow the passage of the polymer, but small enough to remove the impurities from the solution. Representative examples of pore sizes for filters include 1-10 μm .

Soxhlet Extraction

15 A soxhlet extraction can also be used to remove impurities from the polymer, especially if the T_g of the polymer is relatively high (e.g., Pi-BMA, PMMA and PEMA). First, a polymer is placed into a glass extraction tube and the tube is placed inside an extraction apparatus. A solvent is mixed with the polymer. The solvent should be incompatible with the polymer (i.e., does not
20 dissolve the polymer), but should be compatible with one or more impurities. The solvent may cause the polymer to partially swell. Also, typically, the solvent will have a boiling temperature that is below or equal to the T_g of the polymer. In this process, the solvent serves as the extraction medium. Representative examples of polymer-solvent pairs include using methanol for Pi-BMA, ethanol or
25 acetonitrile:methanol (50:50 wt/wt) for PMMA, hexane for PEMA and FLUX

REMOVER AMS for P(BMA-HEMA). After the polymer has been put into solution, a heating source is used to warm the solvent to generate vapor. The solvent vapor removes low molecular weight species from the polymer.

- It has been found that if the temperature exposed to the extraction apparatus is too close to the T_g of the polymer, the polymer can swell and block the filters used in the extraction apparatus. As a result, it may be useful to cool portions of the extraction apparatus (e.g., extraction tube) during the process to prevent polymer swelling.

10 Step Precipitation

- The polymer can also be purified by using a step precipitation process. A polymer mass should first be substantially dissolved in a compatible solvent. While the solution is stirred, an incompatible solvent is gradually added to the solution so that polymer precipitates. The polymer is then recovered and dried.
- 15 The impurities that were in the polymer before the process remain in the solution. In an embodiment, step precipitation is used after centrifugal cleaning wherein the polymer remains dissolved in the solvent used for the centrifugal cleaning process before addition of the incompatible solvents. The following are representative examples of polymer-solvent pairings:

20

Table 2

Polymer	Compatible Solvent(s)	Incompatible Solvent(s)
PBMA	Acetone	Water or Heptane
PEMA	THF	Methanol
P(BMA-HEMA)	THF	Water

Centrifugal Filtration

Impurities can also be removed by centrifugal filtration. This method was originally developed for the removal of cells and particulates from nucleic acids, proteins, and enzymes, and has been adapted for the present invention to remove lower molecular weight fractions from a polymer. First, the polymer is dissolved in a solvent. Then the solution is placed in a centrifugal filtration unit (such as Centriplus-100, available from Millipore, Medford, MA) which is run in a centrifuge (e.g., available from Sorvall, Newtown, CT). The filtration unit should be compatible with the solvent used to dissolve the polymer. In one embodiment, the polymer is first subjected to the centrifugal cleaning process, and then further purified by being placed in the centrifugal filtration apparatus.

Method of Forming the Coating

To fabricate the coating, the purified polymer, or a blend of purified polymers, can be applied on the stent using commonly used techniques known to those having ordinary skill in the art. For example, the polymer can be applied to the stent by dissolving the polymer in a coating solvent, or a mixture of solvents, and applying the resulting solution on the stent by spraying or immersing the stent in the solution.

Representative examples of some suitable coating solvents include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), cyclohexanone, xylene, toluene, acetone, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, *n*-butylacetate, and dioxane. Examples of suitable mixtures of solvents include mixtures of DMAC and methanol (e.g., a 50:50 by mass mixture), cyclohexanone and acetone (e.g.,

80:20, 50:50, 20:80 by mass mixtures), acetone and xylene (e.g., a 50:50 by mass mixture), and acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture). FLUX REMOVER AMS is a trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of
5 a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance methanol, with trace amounts of nitromethane.

In addition, blends of polymers can be used to fabricate the coating. In one embodiment, blends of polyacrylates, such as those listed in Table 1, can be
10 used to fabricate the coating. In another embodiment, a blend of polyacrylates with non-acrylate materials is used. Poly(ethylene-co-vinyl alcohol) (EVAL) is one example of a suitable non-acrylate polymer. EVAL has the general formula — $[\text{CH}_2-\text{CH}_2]_q-[\text{CH}_2-\text{CH}(\text{OH})]_r-$, where “q” and “r” are each an integer. EVAL may also include up to 5 molar % of units derived from styrene, propylene and
15 other suitable unsaturated monomers. A brand of copolymer of ethylene and vinyl alcohol distributed commercially under the trade name EVAL by Aldrich Chemical Co., or manufactured by EVAL Company of America of Lisle, Illinois, can be used.

Examples of other polymers with which polyacrylates can be blended
20 include fluorinated polymers, such as poly(vinylidene fluoride) (PVDF) and poly(vinylidene fluoride-co-hexafluoro propene) (PVDF-HFP). The blend of a polyacrylate and a fluorinated polymer can contain between about 10 and about 95% (mass) of the fluorinated polymer.

Additionally, polymers other than polyacrylates can be used for the
25 coating. Representative examples of suitable alternative polymers include EVAL,

poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane; poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, acrylic polymers and copolymers other than polyacrylates, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene halides (such as polyvinylidene fluoride and polyvinylidene chloride), polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers), polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

The active agent or drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The active agent could be selected, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration

and/or proliferation of smooth muscle cells to inhibit restenosis. Examples of drugs include immunosuppressive substances such as rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of Everolimus available from Novartis), 40-O-tetrazole-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin; and antiproliferative substances such as actinomycin D, or derivatives and analogs thereof. Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin, hydrochloride, and mitomycin. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (ω -3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors),

nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate
5 include alpha-interferon; genetically engineered epithelial cells; tacrolimus; and dexamethasone.

EXAMPLES

Some embodiments of the present invention are illustrated by the
10 following Examples.

Example 1

About 15 grams of PBMA (medical grade, Lot PB 2375 from Esstech, Inc.) was combined with about 185 grams of HPLC grade methanol (available from Aldrich Chemical Co.). The mixture was stirred rigorously for 3 hours, and then
15 the methanol was removed. This procedure was repeated for 5 cycles. After the last cycle, the polymer was vacuum dried at room temperature for about 24 hours to remove residual methanol.

Example 2

A sample of methanol from Example 1 that was removed after washing the
20 polymer was studied to determine if impurities had been removed from the polymer. In particular, a Fourier Transform Infrared Spectrophotometer (available from Perkin-Elmer, Wellesley, MA) was used to compare the spectra from the removed methanol to the spectra of HPLC grade methanol (available

from Aldrich Chemical Co.). Referring to Figure 1, the spectra for the PBMA wash had peaks at 1033 and 1053 cm^{-1} . As shown in Figure 2, however, the spectra for the pure methanol had a peak at 1029 cm^{-1} . Figure 3 is an overlay of the two spectra, while Figure 4 is a subtraction of the two spectra showing that there is a significant peak difference at 1029 cm^{-1} . In short, Figure 4 indicates that an impurity was washed from the polymer in Example 1.

Example 3

The purified polymer from Example 1 was dissolved in acetone (>99.5 % purity, Class 10, Lot C01101, available from General Chemical Corporation, Detroit, MI) at 15% wt/wt. The solution was placed into a 50 ml centrifuge tube and run in a Model 225 Fisher Scientific Centrifuge (available from Fisher Scientific, Houston, TX). The centrifuge was set at a RPM setting of 6 and was run for about 30 minutes. The precipitate containing the impurities was collected and the solution was visually clean. The supernatant was then collected.

Example 4

The purified polymer (i.e., supernatant) from Example 3 was diluted to 2% PBMA in 80:20 acetone/cyclohexanone wt/wt to produce a coating composition. 3x13mm TETRA stents (available from Guidant Corporation) were provided which are made of stainless steel. The stents were cleaned by sonicating for several minutes in de-ionized-water, methanol, then IPA. The stents underwent argon plasma treatment just before being coated.

Thirty-five 3x13mm TETRA stents were coated with the purified polymer composition under the following conditions using a spray coater with an EFD 780S series nozzle: atomization pressure = about 8 psi; feeding pressure = about 3.95 psi; rotation speed = about 60 rpm; no translation motion; nozzle-to-stent distance = about 4.5 cm; spray time = about 2 sec; and waiting until next spray cycle = about 8 sec. After a number of spray cycles, the stents were dried at 70°C for one hour to essentially remove the solvent and form a coating.

12 of the coated stents and 8 bare metal TETRA stents were then crimped onto a balloon catheter apparatus. The stents along with the balloon catheters were then sterilized by ETO for about 12 hours and then aerated for about 48 hours.

Example 5

9 of the coated stents, and 5 of the bare metal stents from Example 4 were used to conduct an animal study. In particular, a 28 day porcine coronary artery model was used to determine if there was a significant biological response from the implantation of PBMA purified according to the methods of the present invention as compared to bare metal (i.e., stainless steel) stents. A standard implantation procedure was used to develop the histology data.

After the stented arteries were removed, they were processed using standard techniques to produce histology slides. Three sections of the stented vessels (i.e., proximal, media and distal) were used in the histology analysis. The percent stenosis was measured. The following Table 3 summarizes the histology data. The data is shown graphically in Figure 5, and Figures 6 (bare metal stents)

and 7 (PBMA coated stents) are sample histology photographs produced by the study.

Table 3

Bare Metal Stents	% Stenosis	Purified PBMA Coated Stents	% Stenosis
1	46.20	1	32.18
2	28.16	2	23.36
3	22.52	3	32.07
4	16.91	4	17.95
5	23.05	5	18.09
		6	26.61
		7	42.75
		8	24.64
		9	26.05
Average % Stenosis	27.37		27.08
Standard Deviation	11.26		7.76

As shown in the data of Table 3, and Figure 5, the area stenosis after 28 days as a result of an implantation of a stent with a purified polymer is substantially equivalent to the area stenosis after 28 days for a stent made of a biocompatible metal. Therefore, the purified polymer was shown to be
5 biologically inert.

Example 6

PBMA ($M_w = 370K$) is dissolved in acetone at 1 gram of PBMA per 5 grams of acetone (wt/wt). The polymer can be agitated or left at room temperature for a number of hours until the polymer become essentially dissolved
10 in the solvent. Some of the low-density particles/aggregates (e.g., suspension agents) may become visible in the solution. The solution can then be exposed to vacuum filtration. The pore size of the filters can be from about $3\mu m$ to about $10\mu m$.

Example 7

PBMA ($M_w = 370K$) is dissolved in acetone at 1:7 (wt/wt). Drops of water/methanol (1:1 wt/wt) are slowly added into the solution while stirring until the rate of polymer precipitation decreases. The precipitated polymer is then recovered and vacuum-dried at $65^\circ C$ for 36 hours. The recovered polymer is then
20 re-dissolved in xylene at 20% (wt/wt) for spray application.

Example 8

PBMA ($M_w = 370K$) is dissolved in ethyl acetate at 15% wt/wt. The solution is placed in a Fisher Scientific Centrifuge, and the centrifuge is run for 30

minutes at a RPM setting of 6. The supernatant is collected. A portion of the supernatant is further diluted to 3% wt/wt and is transferred to a centrifugal filtration unit (available from Millipore). The centrifuge spin speed is set at 9.5 and the solution is centrifuged for about 4 hours. The process can be repeated.

- 5 After about 24 hours of centrifugal filtration, a significant amount of the purified polymer can be collected.

Example 9

A polymer solution is prepared containing about 2.0 mass % of EVAL in the solvent DMAC. The solution is applied onto a stent to form a primer layer.

- 10 To apply the primer layer, a spray apparatus, the EFD 780S spray nozzle with a VALVEMATE 7040 control system, manufactured by EFD, Inc. of East Providence, Rhode Island is used. The EFD 780S spray nozzle is an air-assisted external mixing atomizer. The composition is atomized by air and applied to the stent surfaces. During the process of applying the composition, the stent is rotated
- 15 about its longitudinal axis, at a speed of about 100 rpm. The stent is also linearly moved along the same axis during the application.

- The EVAL solution is applied to a 13-mm TETRA stent (available from Guidant Corporation) in a series of 10-second passes to deposit about 10 μg of coating per spray pass. Between the spray passes, the stent is dried for about 10
- 20 seconds using flowing air with a temperature of about 60°C. Five spray passes are applied, followed by baking the primer layer at about 140°C for one hour. As a result, a primer layer is formed having a solids content of about 50 μg . "Solids" means the amount of the dry residue deposited on the stent after essentially all volatile organic compounds (e.g., the solvent) have been removed.

- 25 A drug-containing formulation is prepared comprising:

(a) about 2.0 mass % of EVAL;

(b) about 1.0 mass % of Everolimus; and

(c) the balance, a solvent mixture of DMAC and pentane, the solvent mixture containing about 80 (mass) % of DMAC and about 20 (mass) % of pentane.

In a manner identical to the application of the primer layer, five spray passes are performed, followed by baking the drug-polymer layer at about 50°C for about 2 hours to form the drug-polymer layer having a solids content of about 90 µg, and a drug content of about 30 µg.

Finally, a topcoat composition to control the drug release rate is prepared having purified PBMA. The PBMA polymer used for this example is first purified by solvent washing using methanol, and then centrifugal cleaning using acetone. The purified PBMA is then added to a solvent system and diluted to provide a 2.0 mass % solution, where the solvent system includes a 10:50:40 (mass) blend of acetone, Techspray's FLUX REMOVER AMS, and xylene. In a manner similar to the application of the primer layer and the drug-polymer layer, a number of spray passes are performed followed by final baking at about 50°C for about 2 hours. As a result, a purified topcoat membrane is formed, the membrane having a solids content of about 50 µg.

Example 10

A primer layer is applied onto an 18-mm TETRA stent using PBMA purified by solvent washing using methanol, and then centrifugal cleaning using acetone. A drug formulation is prepared comprising:

- (a) about 2.0 mass % of PBMA also purified by solvent washing using methanol, and then centrifugal cleaning using acetone;
- (b) about 1.6 mass % of Everolimus; and
- (c) the balance, a solvent system having a 60:40 (mass) blend of acetone and xylene.

The drug formulation is applied onto the stent, and a drug-polymer layer is formed in a manner similar to that described in Example 9. The solids content of the drug-polymer layer is about 1,000 µg. In this Example, the stent coating has no separate topcoat membrane.

10

Example 11

A primer layer is applied onto an 18-mm TETRA stent as described in Example 10. A drug formulation is then prepared including:

- (a) about 2.0 mass % of P(MMA-BMA) having a weight-average molecular weight (M_w) of about 150,000 available from Aldrich Chemical Company. Before the P(MMA-BMA) polymer is added to the formulation, the polymer is purified by first washing with methanol and then extracting with soxhlet extraction using Techspray's FLUX REMOVER AMS for about 12 hours;
- (b) about 1.0 mass % of Everolimus; and
- (c) the balance, a solvent system including a 10:50:40 (mass) blend of acetone, FLUX REMOVER AMS and xylene.

20

The P(MMA-BMA) contains about 79.2 mass % of units derived from BMA. The drug formulation is applied onto the dried primer layer, and a drug-polymer layer is formed, in a manner similar to that described in Example 9. The

drug-polymer layer has the total amount of solids of about 520 μg . In this Example, the stent coating has no separate topcoat membrane.

Example 12

A primer layer and a drug-polymer layer are applied onto an 18-mm TETRA stent as described in Example 9. A blend of P(MMA-BMA) and PBMA is then purified by washing in methanol and then centrifugal cleaning with acetone as the solvent. A topcoat composition to control the drug release rate is prepared, having about 2.0 mass % of a 1:1 (by mass) blend of purified P(MMA-BMA) and PBMA, and the balance of a solvent system, the solvent system including a 10:50:40 (mass) blend of acetone, FLUX REMOVER AMS and xylene. The P(MMA-BMA)/PBMA blend can have about 83.3 mass % of units derived from BMA. The topcoat membrane is formed having the total amount of solids of about 30 μg .

Example 13

A primer layer is applied onto an 18-mm TETRA stent as described in Example 10. A drug formulation is then prepared including:

- (a) about 2.0 mass % of PBMA-HEMA ($n/m = 7/3$). Before the PBMA-HEMA polymer is added to the formulation, the polymer is purified by first washing with methanol and then centrifugal cleaning using acetone;
- (b) about 1.6 mass % of Everolimus; and
- (c) the balance, a solvent system including a 70:30 (mass) blend of acetone and xylene.

The drug formulation is applied onto the dried primer layer to form the drug-polymer layer. The drug-polymer layer has the total amount of solids of

about 600 µg. In this Example, the stent coating has no separate topcoat membrane.

Example 14

A primer layer and a drug-polymer layer are applied onto an 18-mm
5 TETRA stent as described in Example 9. A select amount of PEMA is then
purified by first washing with methanol and then extracting with soxhlet
extraction using FLUX REMOVER AMS for about 12 hours. A topcoat
composition to control the drug release rate is prepared, having about 2.0 mass %
of purified PEMA, and the balance a solvent system including a 80:20 (mass)
10 blend of acetone and cyclohexanone. PEMA having a weight-average molecular
weight M_w of about 101,400 available from Aldrich Chemical Company is one
example of a brand of PEMA that can be used.

The topcoat composition is applied onto the dried drug-polymer layer.
A number of spray passes are performed followed by final baking, at about 80°C
15 for about 1 hour. The topcoat membrane is formed having a solids content of
about 40 µg.

While particular embodiments of the present invention have been shown
and described, it will be obvious to those skilled in the art that changes and
20 modifications can be made without departing from this invention in its broader
aspects. Therefore, the appended claims are to encompass within their scope all
such changes and modifications as fall within the true spirit and scope of this
invention.

CLAIMS

WHAT IS CLAIMED IS:

1. A stent used for implantation in a vessel of a patient, comprising a coating, the coating including a polymeric material which has been purified to be
5 completely or partially free from an impurity or impurities which cause the material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material.
2. The stent of Claim 1, wherein the polymeric material is selected from a
10 group consisting of poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(methyl acrylate), poly(*n*-hexyl methacrylate), poly(methyl methacrylate-co-*n*-butyl methacrylate), poly(*n*-butyl methacrylate-co-*iso*-butyl methacrylate), poly(*n*-butyl methacrylate-co-2-
15 hydroxyethyl methacrylate), poly(methyl methacrylate-co-2-hydroxyethyl methacrylate) and poly(ethyl methacrylate-co-2-hydroxyethyl methacrylate)..
3. The stent of Claim 1, wherein the polymeric material is a polyacrylate material.
4. The stent of Claim 1, wherein the coating includes at least two layers,
20 wherein the outer most layer of the coating is made from the purified polymeric material.
5. The stent of Claim 1, wherein the coating includes at least two layers, wherein at least one of the layers includes an active agent for the treatment of restenosis, wherein at least one of the layers is made from the purified polymeric

material, and wherein the purified polymeric material includes a polyacrylate material.

6. The stent of Claim 1, wherein the polymeric material includes poly(*n*-butyl methacrylate) and the coating additionally comprises rapamycin or functional

5 analog or structural derivative thereof.

7. The stent of Claim 1, wherein the coating additionally comprises an active agent.

8. The stent of Claim 7, wherein the active agent is rapamycin, or derivatives or analogs thereof.

10 9. The stent of Claim 1, wherein the polymeric material is a blend of at least two polymers.

10. A method of coating a stent comprising forming a coating including a polymeric material on the stent, wherein the polymeric material has been purified to remove, or reduce the amount of, an impurity or impurities which cause the
15 material to have a greater adverse biological response than the response caused by the material when the impurity or impurities have been removed or reduced from the material.

11. The method of Claim 10, wherein the polymeric material is selected from a group consisting of poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate),

20 poly(*tert*-butyl methacrylate), poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(methyl acrylate), poly(*n*-hexyl methacrylate), poly(methyl methacrylate-co-*n*-butyl methacrylate), poly(*n*-butyl methacrylate-co-*iso*-butyl methacrylate), poly(*n*-butyl methacrylate-co-2-hydroxyethyl methacrylate), poly(methyl methacrylate-co-2-hydroxyethyl
25 methacrylate) and poly(ethyl methacrylate-co-2-hydroxyethyl methacrylate).

12. The method of Claim 10, wherein the polymeric material is poly(*n*-butyl methacrylate) and the coating additionally comprises rapamycin or functional analog or structural derivative thereof.
13. The method of Claim 10, wherein the coating additionally includes an active agent.
14. The method of Claim 10, wherein the polymeric material is purified by a process selected from the group consisting of solvent washing, centrifugal cleaning, soxhlet extraction, filtration, step precipitation, centrifugal filtration and a combination thereof.
15. A method of coating a stent, comprising: purifying a polymeric material to partially or completely remove an impurity or impurities which can cause an adverse biological response; adding the purified polymeric material to a solvent to form a composition; applying the composition to the stent; and removing the solvent to form a coating including the purified polymeric material.
16. The method of Claim 15, additionally comprising adding an active agent to the composition.
17. The method of Claim 15, wherein the polymeric material is purified by a process including dissolving the material in a solvent and subjecting the material to the rotational motion of a centrifuge device.
18. The method of Claim 15, wherein the polymeric material is purified by a process including combining the material having a first impurity with a first solvent, wherein the material is substantially insoluble in the first solvent and the first impurity is substantially soluble in the first solvent to substantially or completely remove the first impurity from the material.

19. The method of Claim 18, further including, subsequent to removing the first impurity from the material, dissolving the material in a second solvent and subjecting the material to the rotational motion of a centrifuge device.

20. The method of Claim 18, wherein the material has a second impurity and

5 further including combining a second solvent with the material, wherein the material is substantially insoluble in the second solvent and the second impurity is substantially soluble in the second solvent to substantially or completely remove the second impurity from the material.

21. A stent comprising a coating, the coating including a purified polymeric

10 material that has generally the same degree of biological inertness as stainless steel when implanted in a blood vessel of a mammal.

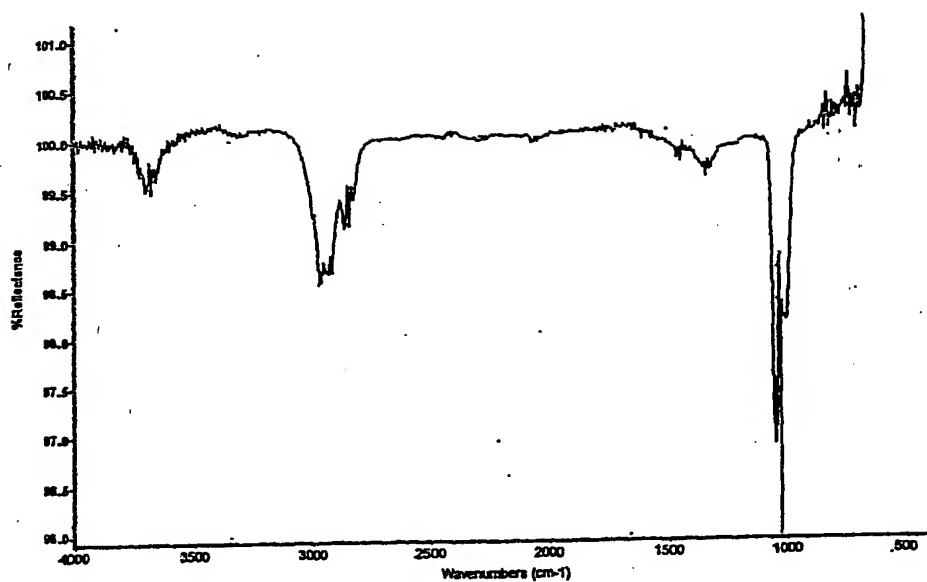


FIGURE 1

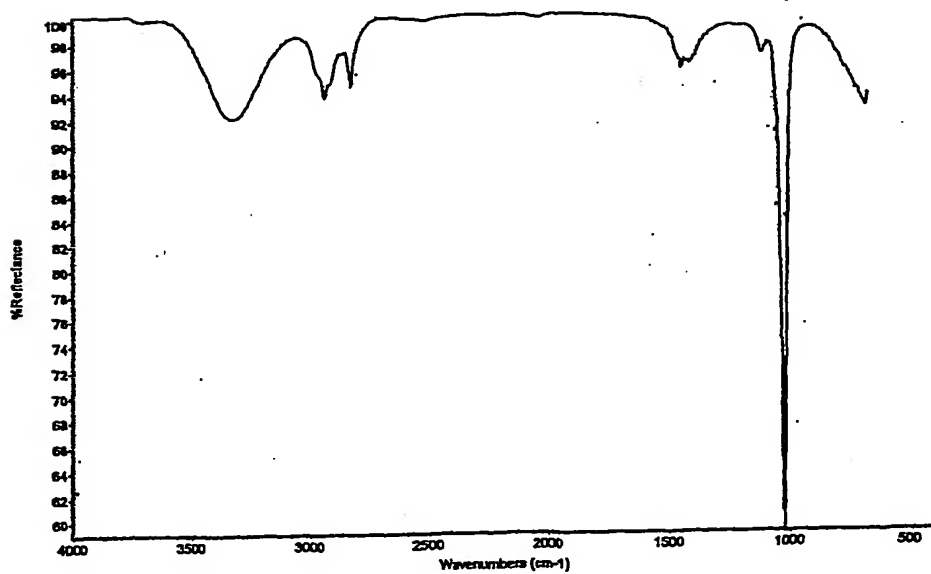


FIGURE 2

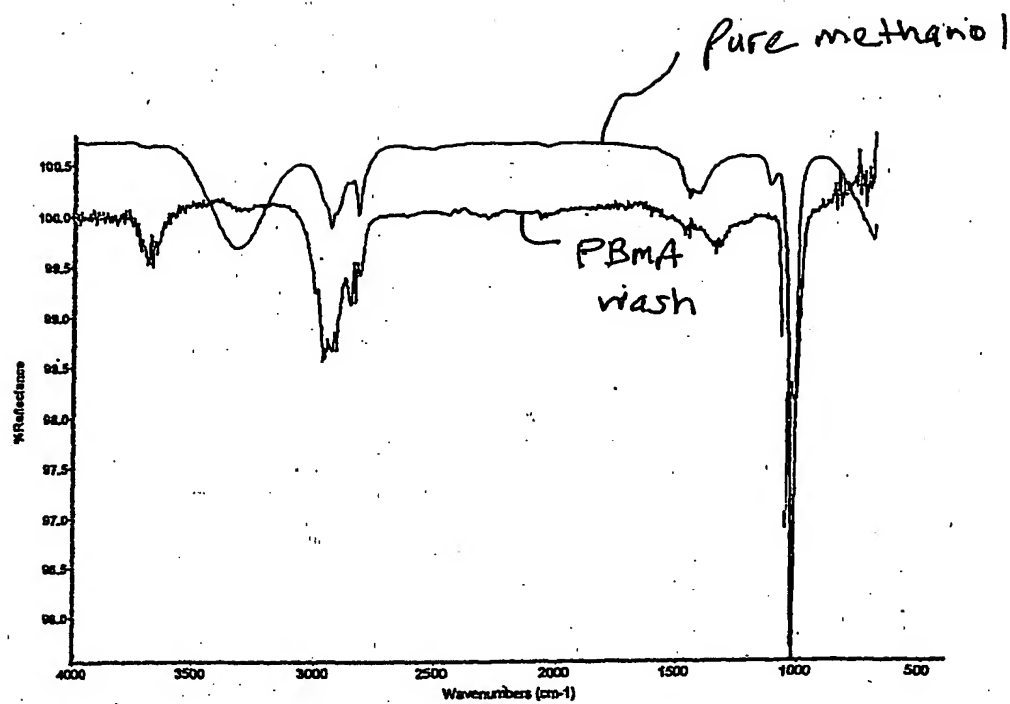


FIGURE 3

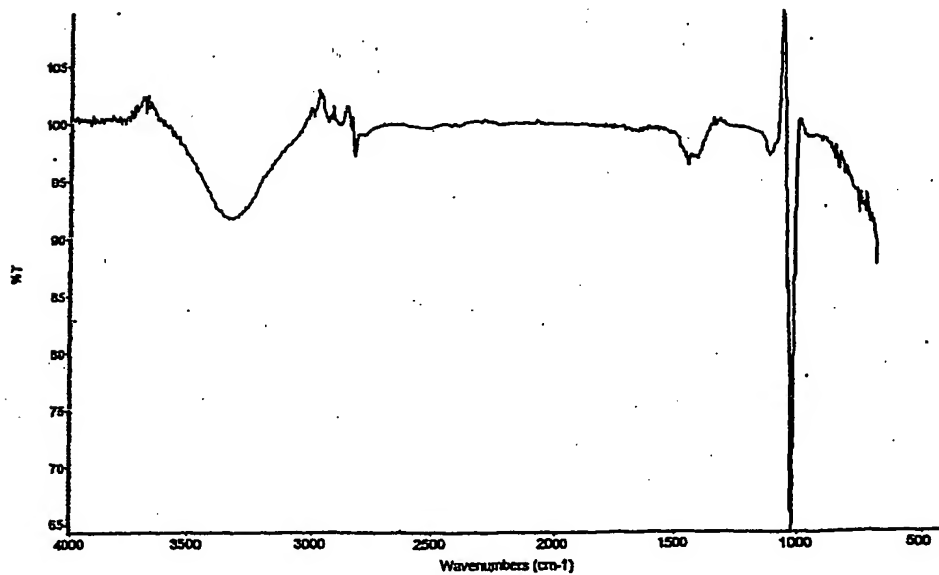


FIGURE 4

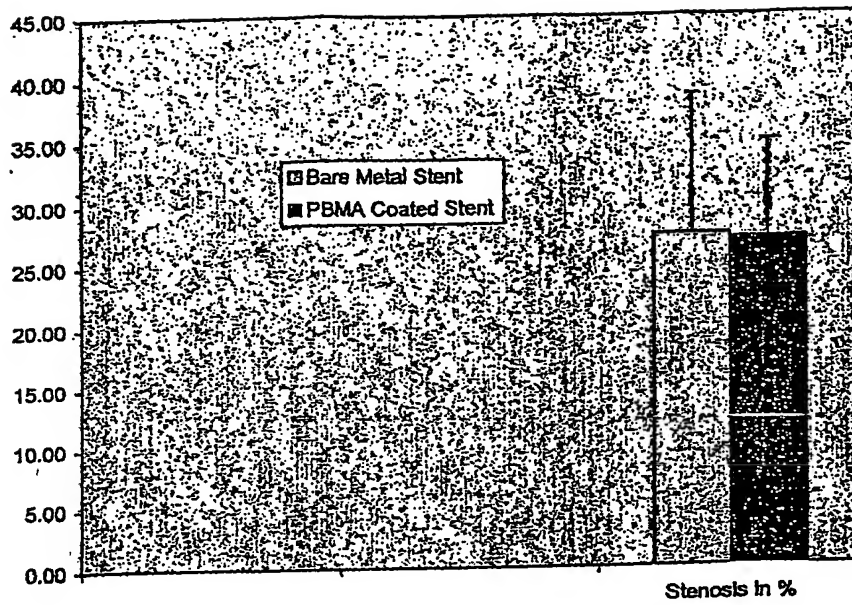


Figure 5

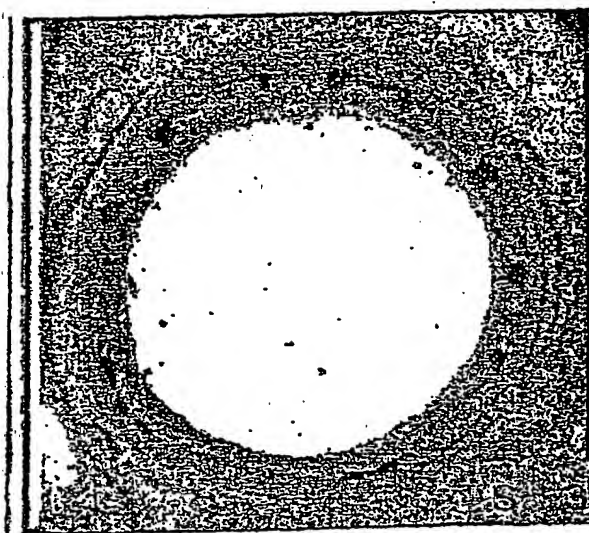


Figure 6

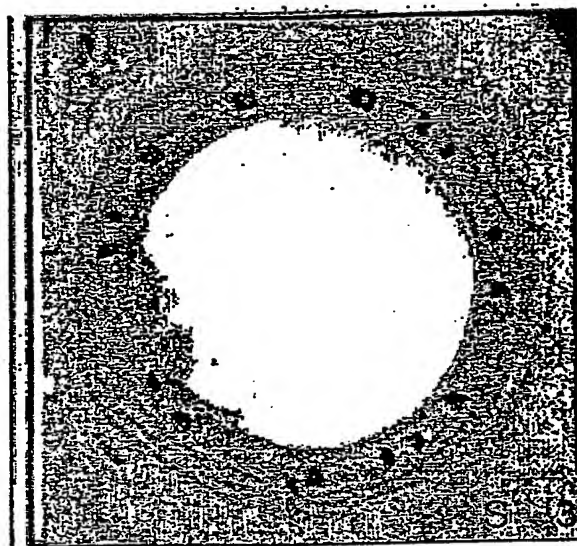


Figure 7

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/21170

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61L31/10 A61L27/34 C08L33/08 C08L33/10 C08L33/12 C08F6/00 C08F6/08 C08F6/10		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61L C08L C08F		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 562 734 A (KING RICHARD S) 8 October 1996 (1996-10-08) column 2, line 9 - line 20	1-21
Y	WO 01 87372 A (CORDIS CORP) 22 November 2001 (2001-11-22) example 2	1-21
X	WO 00 02599 A (BINDERMAN ITZHAK ;ADVANCED BIOCOMPATIBLE COATING (US)) 20 January 2000 (2000-01-20) claim 26; examples 1,2	1-4,10, 11,14
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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Date of the actual completion of the international search 24 October 2003		Date of mailing of the international search report 31/10/2003
Name and mailing address of the ISA European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Vandenbogaerde, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CIFKOVA I ET AL: "IRRITATION EFFECTS OF RESIDUAL PRODUCTS DERIVED FROM POLY-2-HYDROXYETHYL METHACRYLATE GELS II. COMPOUNDS EXTRACTED FROM HYDROGELS" BIOMATERIALS, vol. 9, no. 4, 1988, pages 372-375, XP009019663 ISSN: 0142-9612 page 3; table 3	1-21
A	WO 99 55396 A (SURMODICS INC) 4 November 1999 (1999-11-04) abstract	1-21

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/21170

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5562734	A	08-10-1996	CN 1138489 A	25-12-1996
			GB 2301594 A , B	11-12-1996
WO 0187372	A	22-11-2001	AU 5977401 A	26-11-2001
			AU 6157901 A	26-11-2001
			AU 6158001 A	26-11-2001
			AU 6158101 A	26-11-2001
			AU 6295701 A	26-11-2001
			AU 6311201 A	26-11-2001
			AU 6311301 A	26-11-2001
			CA 2408606 A1	22-11-2001
			CA 2408608 A1	22-11-2001
			CA 2408719 A1	22-11-2001
			CA 2408729 A1	22-11-2001
			CA 2408752 A1	22-11-2001
			CA 2408754 A1	22-11-2001
			CA 2408838 A1	22-11-2001
			EP 1280568 A1	05-02-2003
			EP 1280569 A1	05-02-2003
			EP 1280570 A2	05-02-2003
			EP 1280571 A1	05-02-2003
			EP 1289576 A1	12-03-2003
			EP 1280512 A2	05-02-2003
			EP 1280572 A1	05-02-2003
			WO 0187372 A1	22-11-2001
			WO 0187373 A1	22-11-2001
			WO 0187374 A1	22-11-2001
			WO 0187342 A2	22-11-2001
			WO 0187375 A1	22-11-2001
			WO 0187263 A2	22-11-2001
			WO 0187376 A1	22-11-2001
			US 2001029351 A1	11-10-2001
			US 2002016625 A1	07-02-2002
			US 2002007213 A1	17-01-2002
			US 2002007214 A1	17-01-2002
			US 2002007215 A1	17-01-2002
			US 2002005206 A1	17-01-2002
WO 0002599	A	20-01-2000	AU 4645299 A	01-02-2000
			WO 0002599 A1	20-01-2000
WO 9955396	A	04-11-1999	AT 219693 T	15-07-2002
			AU 760408 B2	15-05-2003
			AU 3563899 A	16-11-1999
			CA 2320259 A1	04-11-1999
			DE 69901927 D1	01-08-2002
			DE 69901927 T2	10-10-2002
			DK 1019111 T3	14-10-2002
			EP 1174157 A1	23-01-2002
			EP 1019111 A1	19-07-2000
			ES 2179646 T3	16-01-2003
			JP 3406903 B2	19-05-2003
			JP 2002512856 T	08-05-2002
			PT 1019111 T	31-10-2002
			WO 9955396 A1	04-11-1999
			US 2003031780 A1	13-02-2003
			US 6214901 B1	10-04-2001
			US 6344035 B1	05-02-2002

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/21170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955396	A	US 2002032434 A1	14-03-2002

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